REMARKS

Reconsideration of the present application is respectfully requested in view of the above amendments and the following remarks. Claims 21, 23-26, 30-33, and 36-48 are currently pending. The Examiner has withdrawn claims 25, 26, 30-33, and 44-48. Claims 21, 23, 24, and 36-43 are currently under examination. Claims 21, 23, 36-38, 40, and 42 currently under examination and withdrawn claims 30 and 33 have been amended to point out with greater particularity and to claim distinctly certain embodiments of Applicants' invention. No new matter has been added to the application by these amendments. Support for the amendments may be found throughout the application, for example, at page 18, lines 8-15 and lines 30-33; page 19, lines 13-15, lines 24-31; page 20, lines 10-12 and 14; and page 30, lines 21-34.

The specification has been amended to change the verb tense from past to present in Example 5 (paragraph beginning at page 59, line 11) and in Example 7 (paragraph beginning at page 61, line 10). These Examples have been amended to indicate that the examples outline steps of protocols and procedures that may be performed. No new subject matter has been added by these amendments.

As an initial matter, Applicants respectfully request clarification with respect to the manner in which the Examiner is interpreting the claim language. In the Office Action (dated July 11, 2008) (*see* page 4, second paragraph; page 6, lines 4-5), the phrase, "90% or 95% or antigenic fragment of at least 15 contiguous amino acids of SEQ ID NO:2 are viewed as variants/fragments of SEQ ID NO:2," is placed within quotation marks as though a claim feature, at least in part, is being recited. However, the recitation in quotes has never been recited in any claim.

Applicants are further confused by a passage in the discussion of enablement (*see* Action, page 7, second full paragraph), which states that recitation "of the phrase 'an amino acid sequence' reads upon fragments of SEQ ID NO:2, since 15 amino acids from SEQ ID NO:2 is merely one interpretation of 'an amino acid sequence of SEQ ID NO:2.'" Applicants submit that when the phrase "an amino acid sequence" is recited in the present claims, the phrase must be read and interpreted within the context of the entire claim and in a manner as set forth by the clear and plain language. Applicants understand that the U.S. Patent and Trademark Office (PTO) interprets the phrase, "an amino acid sequence," to mean less than full-length SEQ ID

NO:2, *but only if* the recitation were "an amino acid sequence as set forth in SEQ ID NO:2." This is not the phrase recited in the present claims.

While Applicants are unclear with respect to the Examiner's meaning in the Office Action and consequent interpretation of the claims, Applicants submit that when the claims refer to a polypeptide consisting of "*an amino acid sequence* at least 90% identical to *the* amino acid sequence set forth as SEQ ID NO:2," for example, the claim does not encompass a fragment of a polypeptide at least 90% identical to SEQ ID NO:2. Given that SEQ ID NO:2 contains 178 amino acids, a polypeptide that consists of *an amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:2* can be no less than 160 amino acids (*i.e.,* 90% of 178). To interpret the claim as though smaller polypeptide fragments are included essentially requires inserting a new phrase into the claim, as shown in italics: "a polypeptide that comprises an amino acid sequence *of an amino acid sequence* that is at least 90% identical to the amino acid sequence of SEQ ID NO:2."

This reading of the claim is contrary to how a person skilled in the art reads the claims, and is thus improper (see *In re Cortright*, 165 F.3d 1353, 1358 (Fed. Cir. 1999) ("Although the PTO must give claims their broadest reasonable interpretation, this interpretation must be consistent with the one that those skilled in the art would reach.")). A person skilled in the art would not read a claim that recites "an isolated polypeptide comprising an amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:2" to encompass a polypeptide that has less than 90% identity to SEQ ID NO:2. Such an interpretation is not only nonsensical, but renders claiming a genus of polypeptides by reciting any percent identity to a reference polypeptide, impossible. Furthermore, such an interpretation is contrary to how the PTO has previously interpreted such language when issuing scores of claims reciting this language as used in the present claims (*see id.* at 1358 ("Accordingly, the PTO's interpretation of claim terms should not be so broad that it conflicts with the meaning given to identical terms in other patents from analogous art.")).

Nevertheless and even though unnecessary, Applicants have amended claims 23, 36, 38, and 40 for additional clarity,. The amended claims recite that the polypeptide comprises (or consists of) an amino acid sequence at least 90% or 95% identical to **the full-length** amino acid sequence set forth in SEQ ID NO:2. When a claim submitted herewith refers to a

polypeptide fragment, the claims explicitly recite the minimum length of the polypeptide fragment, the full-length polypeptide sequence from which the fragment is obtained, and also recite functional characteristics of the polypeptide fragment. The following remarks that pertain to these claims and claims dependent thereon for all rejections are based on the proper reading of the claims.

REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH (WRITTEN DESCRIPTION—NEW MATTER)

The Examiner rejected claims 21, 24, 37, 42, and 43 under 35 U.S.C. U.S.C. § 112, first paragraph, for allegedly introducing new matter that is not supported by the specification as filed. The Examiner asserts that the specification does not clearly support the chimeric polypeptides.

Applicants respectfully traverse this rejection and submit that the claimed chimeric polypeptides are adequately described in the specification as filed. The present claims relate in one embodiment (see present claim 21) to a chimeric polypeptide comprising two or more antigenic polypeptide fragments of a polypeptide consisting of the amino acid sequence set forth in SEQ ID NO:2, wherein the two or more antigenic polypeptide fragments each comprise at least 15 contiguous amino acids of SEQ ID NO:2 and are linked to form an immunogenic chimeric polypeptide, wherein the two or more antigenic polypeptide fragments elicit an antibody that specifically binds to a polypeptide that consists of the amino acid sequence set forth as SEQ ID NO:2 and induces an immune response against *Streptococcus pyogenes*. In another embodiment (see present claim 42), a chimeric polypeptide comprises an antigenic fragment that consists of at least 15 contiguous amino acids of SEQ ID NO:2, wherein the antigenic fragment elicits an antibody that specifically binds to a polypeptide consisting of the amino acid sequence set forth as SEQ ID NO:2 and induces an immune response against *S. pyogenes*.

The polypeptide comprising the amino acid sequence set forth as SEQ ID NO:2 (referred to in the application as SHB-GAS-102) was isolated and identified as being present in multiple serotypes of *Streptococcus pyogenes* (*see, e.g.,* page 48, line 18 through page 54, line 4 (Example 1)). SHB-GAS-102 is immunogenic and is capable of inducing antibodies that

provided passive immunity against lethal *S. pyogenes* challenge, and also is capable of inducing an immune response against *S. pyogenes* that actively immunized animals against lethal challenge with *S. pyogenes* (*see, e.g.,* page 63-64 (Example 9)).

The present specification describes that a chimeric polypeptide may comprise one or more polypeptides, or fragments of these polypeptides, described in the figures of the present application, which includes Figure 2 that presents the amino acid sequence of SEQ ID NO:2 (*see, e.g.,* page 28, lines 25-28; Figure 2). The specification also describes that a chimeric polypeptide may comprise two or more polypeptides, including the polypeptide comprising SEQ ID NO:2, or fragments thereof (*see, e.g.,* page 28, lines 30-34). Also as described in the specification, a polypeptide fragment may be at least 15 contiguous amino acids of a *S. pyogenes* polypeptide (*see, e.g.,* page 19, lines 23-25, and at page 20, lines 10-13).

As described in the application, polypeptides include fragments of SHB-GAS-102 (*see, e.g.,* page 16, lines 24-30; page 17, lines 29-21). An antigenic fragment of the polypeptide consisting of the amino acid sequence of SEQ ID NO:2 comprises at least one antigenic region (or epitope) (*see, e.g.,* page 19, lines 13-15; page 29, lines 8-10). Thus, antigenic fragments retain the immunogenic and antigenic properties of SHB-GAS-102 (*see, e.g.,* page 19, line 33 through page 20, line 2); that is, the fragments retain the capability to induce an immune response in a host and to elicit antibodies that specifically bind to the full-length polypeptide of SEQ ID NO:2 (*see, e.g.,* page 18, lines 8-20; *see also* page 18, lines 22-33; page 26, lines 14-21).

The specification further describes pharmaceutical compositions that comprise the chimeric polypeptides (*see, e.g.,* page 31, lines 29-32; page 32, lines 1-4; original claim 24; *see also, e.g.,* page 32, line 33 through page 33, line 4). Support for the claimed kit that comprises a chimeric polypeptide comprising at least two or more antigenic polypeptide fragments of any one of the polypeptides described in the application, including SHB-GAS-102, may be found in original claim 37 and in the specification (*see, e.g.,* page 48, lines 4-6).

Applicants therefore submit that the present claims do not include new matter and have support in the specification as originally filed in accordance with the requirements under 35 U.S.C. § 112, first paragraph. Applicants respectfully request withdrawal of this rejection.

REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH (WRITTEN DESCRIPTION)

The Examiner rejected claims 21, 23, 24, 36-38, 40, and 42-43 under 35 U.S.C. U.S.C. § 112, first paragraph, for allegedly failing to comply with the written description requirement. The Examiner asserts that the specification does not describe relevant, identifying structural and functional characteristics of species within the claimed genus to convey to a person skilled in the art that Applicants possessed the claimed genus at the time of filing the application.

Applicants traverse this rejection and submit that the instant claims satisfy the written description requirement under 35 U.S.C. § 112, first paragraph. The presently claimed embodiments relate, in pertinent part, to a chimeric polypeptide comprising two or more antigenic polypeptide fragments of a polypeptide consisting of the amino acid sequence set forth in SEQ ID NO:2, wherein the two or more antigenic polypeptide fragments each comprise at least 15 contiguous amino acids of SEQ ID NO:2 and are linked to form an immunogenic chimeric polypeptide; to a chimeric polypeptide comprising an antigenic fragment that consists of at least 15 contiguous amino acids of SEQ ID NO:2; and to compositions and kits comprising these chimeric polypeptides. As recited in the present claims, an antigenic polypeptide fragment is capable of eliciting an antibody that specifically binds to the polypeptide consisting of the amino acid sequence set forth as SEQ ID NO:2, and inducing an immune response against *S. pyogenes*. In another embodiment, the present claims relate, in pertinent part, to a pharmaceutical composition comprising an isolated polypeptide that consists of an amino acid sequence at least 90% identical to the full-length amino acid sequence set forth as SEQ ID NO:2 or that comprises an amino acid sequence at least 95% identical to the full-length amino acid sequence set forth as SEQ ID NO:2, wherein the isolated polypeptide elicits an antibody that specifically binds to a polypeptide consisting of the amino acid sequence set forth as SEQ ID NO:2 and that induces an immune response against *S. pyogenes*.

Written description is adequate when the specification describes the claimed embodiments in sufficient detail to convey *to a person skilled in the art* that the Applicants were in possession of the claimed embodiments at the time of filing, even if each and every species encompassed by the claims is not explicitly described in the specification. *See, e.g., Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991) citing *In re Gosteli*, 872 F.2d 1008, 1012

(Fed. Cir. 1989) ("Although [the applicant] does not have to describe exactly the subject matter claimed, … the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed."). The Federal Circuit Court of Appeals has articulated that with respect to the biological art, "[p]recedent illustrates that the determination of what is needed in a specification to support generic claims related to biological subject matter depends on a variety of factors, including existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, the predictability of the aspect at issue, and other considerations appropriate to the subject matter" (*Capon v. Eshhar,* 418 F.3d 1349, 1359 (Fed. Cir. 2005), citing *In re Wallach*, 378 F.3d 1330, 1333-34 (2004); *University of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 925 (Fed. Cir. 2004); *Singh v. Brake*, 317 F.3d 1334, 1343 (Fed. Cir. 2003)); (*see also* M.P.E.P. § 2163.02)).

Therefore, the fundamental inquiry under the written description requirement focuses on the knowledge of a person skilled in the art. *See also* M.P.E.P. § 2163.02. From this perspective, and contrary to the Examiner's assertion, the instant specification conveys sufficiently detailed, relevant identifying characteristics of the presently claimed chimeric polypeptides and related compositions, and compositions comprising a polypeptide comprising the amino acid sequence set forth as SEQ ID NO:2 (referred to as SHB-GAS-102) and highly related variants thereof, to a person skilled in the art, such as by correlating the recited structural features of the polypeptides and chimeric polypeptides with the recited functional features. See *Enzo Biochem v. Gen-Probe*, 323 F.3d 956, 964, 967, 968 (Fed. Cir. 2002).

Patent applicants are not required to disclose every species encompassed by the claims, even in an unpredictable art (*see In re Angstadt*, 537 F.2d 498, 502-03 (CCPA 1976)). The written description requirement can be met by "show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics … *i.e.,* complete or partial structure, other physical and/or chemical properties, *functional characteristics when coupled with a known or disclosed correlation between function and structure*, or some combination of such characteristics" (*see Enzo Biochem., Inc. v. Gen-Probe Inc.*, 323 F.3d 956, 964 (Fed. Cir. 2002) (citing the U.S. Patent and Trademark Office Guidelines, 66 Fed. Reg. at 1106) (emphasis added); *see also* M.P.E.P. § 2163(II)(A)(3)(a)). Therefore, the written description requirement may be met for a genus if the specification adequately correlates the claimed structure and

function for the members of the genus. A small number of species may thus adequately describe a genus, so long as the disclosure sets forth adequate details regarding the relevant characteristics of the genus.

The SHB-GAS-102 polypeptide is a conserved polypeptide expressed by different serotype strains of *S. pyogenes* (*see, e.g.,* page 48, line 19 through page 54, line 4 and Tables 2 and 3 (Example 1)). The specification describes the detailed, primary amino acid sequence of a SHB-GAS-102 polypeptide (see Figure 2; SEQ ID NO:2). The claims recite that in certain embodiments, the SHB-GAS-102 polypeptide has a structure that consists of an amino acid sequence at least 90% identical to SEQ ID NO:2 or that comprises an amino acid sequence at least 95% identical to the amino acid sequence set forth as SEQ ID NO:2. As described in the specification and recited in the present claims, a chimeric polypeptide may comprise at least one or at least two antigenic fragments of the SHB-GAS-102 polypeptide consisting of SEQ ID NO:2, which fragments comprise at least one antigenic region (or epitope) (*see, e.g.,* page 19, lines 13-15; page 29, lines 8-10) and consist of at least 15 consecutive amino acids (*see, e.g.,* page 19, lines 23-25, and at page 20, lines 10-13).

The application further describes certain functional features that correlate with the described and recited structural features of a SHB-GAS-102 polypeptide and antigenic fragments thereof. As described in the application, polypeptides include fragments of SHB-GAS-102 (*see, e.g.,* page 16, lines 24-30; page 17, lines 29-21), which polypeptides and fragments thereof are immunogenic, that is, capable of inducing an immune response in a host and eliciting antibodies that specifically bind to the full-length polypeptide of SEQ ID NO:2 (*see, e.g.,* page 18, lines 8-20; *see also, e.g.,* page 18, lines 22-33; page 26, lines 14-21). As described in working examples, the SHB-GAS-102 polypeptide (1) induced an immune response that included eliciting polyclonal antibodies that that bind specifically to the SHB-GAS-102 polypeptide; (2) induced an immune response in rabbits that included eliciting polyclonal antibodies used to protect a host (*i.e.,* passive immunity) from lethal challenge by *S. pyogenes*; and (3) induced an immune response that protected animals from infection in an art-accepted animal model (*i.e.,* active immunity) (*see* page 61, line 9 through page 62, line 25 (Example 8); page 63, line 1 through page 64 (Example 9)).

The "written description requirement serves a teaching function, a "*quid pro quo*" in which the public is given "meaningful disclosure in exchange for being excluded from practicing the invention for a limited period of time." See *University of Rochester v. Searle*, 358 F.3d 916, 922 (Fed. Cir. 2004) (emphasis added), quoting *Enzo*, 323 F.3d at 970. By providing the exemplary amino acid sequence of the SHB-GAS-102 polypeptide, describing that this polypeptide is conserved and expressed by different strains of *S. pyogenes*, and demonstrating that the polypeptide induces an immune response against *S. pyogenes*, which includes a protective immune response, Applicants have provided sufficient, meaningful disclosure and are entitled to claims of sufficient scope that adequately protect Applicant's inventive efforts.

Description of the full-length amino acid sequence of SHB-GAS-102 is sufficiently meaningful to a person skilled in the art when, as here, an antigen induces a polyclonal antibody response. Contrary to the assertion by the Examiner (see Action, paragraph bridging page 4 and 5), a person skilled in the art need not be able to predict with certainty, which amino acid (if any), if it were substituted or deleted would abrogate immunogenicity of the an SHB-GAS-102 polypeptide. Capability to induce a polyclonal response, by definition, indicates that the antigen has multiple immunoepitopes. As described in the specification, animals immunized with the exemplary SHB-GAS-102 polypeptide induced an immune response that provided statistically significant protection from lethal *S. pyogenes* infection (*see, e.g.,* Table 5; pages 63-64). Thus, the SHB-GAS-102 immunogen was demonstrated by Applicants to induce an effective polyclonal antibody response.

According to textbook knowledge, "the number of different antibodies which may be produced to an antigen is *high*" and "[d]ifferent antibodies to an antigen often bind to epitopes which overlap on the antigen surface" (emphasis added) (Roitt et al., *Immunology*, 1998, 4th Edition, Mosby, London, page 7.7), submitted herewith). The state of the art is also exemplified by Lipman, teaching that "because [polyclonal antibodies] are heterogeneous and recognize a host of antigenic epitopes, the effect of change on a single or small number of epitopes is less likely to be significant" (Lipman et al., *ILAR Journal*, 46: 258-268, 261, Col. 1 (2005) (enclosed herewith for the Examiner's convenience)). Because the specification describes that the SHB-GAS-102 polypeptide induced a polyclonal antibody response, a person skilled in the art would have readily appreciated at the time of filing that polypeptides having an

amino acid sequence differing from SEQID NO:2 by no more than 5% or 10%, either due to spontaneous mutations occurring in a natural environment or to recombinantly introduced mutations, will *more likely than not* retain the claimed correlative immunologic functions. Thus, given the description in the application and the understanding in the art, Applicants have provided sufficiently meaningful disclosure for a person skilled in the art to practice the full scope of the instant claims.

In addition, the advanced state of the art at the time of filing demonstrates that to identify highly related polypeptide variants that *retain* their functional characteristics is *more predictable* than to identify those that lose their functional characteristics. Contrary to the Examiner's discussion, this degree of predictability applies even in the absence of specific knowledge of amino acids that may or may not be changed (*see* the Action, page 4). One highly illustrative example of the "predictability" of identifying *functional* polypeptide variants may be found in Wan et al. (*Mol. Endocrinol.* 17:2240-50 (2003) enclosed herewith) (Wan), which describes the process of screening for variants that retained function (binding to a monoclonal antibody) and variants that lost this function. In particular, Wan prepared a library of 5200 random polypeptide variants, without consideration for tolerant or intolerant amino acids, and detected only 125 variants (less than 2.5%) that no longer specifically bound to a specific antibody. By quantifying the number of random polypeptide variants that retain or lose the ability to bind a single, specific antibody, the teachings in Wan reasonably reflect the "predictability" of the art with regard to the expectation that polypeptide variants would retain the immunogenic features of a reference polypeptide (*e.g.,* variants that have at least 90% identity to the reference polypeptide).

Wan thus provides evidence that the function of protein is retained following amino acid substitutions and that functional variants of a polypeptide can predictably be made. However, predicting which, if any, single amino acid in the SHB-GAS-102 polypeptide if mutated would abrogate binding of each and every antibody within a pool of polyclonal antibodies, is difficult. Moreover, to meet the written description requirements, Applicants are not required to identify species that are not encompassed by the claimed genus.

The knowledge and understanding in the art also illustrates that persons skilled in the art could use the primary amino acid sequences of SEQ ID NO:2 to identify, with reasonable

accuracy and predictability, amino acid sequences that comprises immunogenic epitopes. Numerous analytical and software tools to identify immunogenic epitopes contained within a primary amino acid sequence were well-known in the art long before the filing date of the instant application. For instance, given the exemplary amino acid sequence of SEQ ID NO:2, a person skilled in the art could use software tools such as PSORT (released in 1991) and Spscan (Wisconsin Sequence Analysis Package, Genetics Computer Group) to predict transmembrane segments and membrane topology of bacterial outer membrane polypeptides. These tools are helpful because a person skilled in the vaccine art understands that immunodominant regions of an antigen are located at exposed areas on the exterior face of the antigen, particularly where loops of polypeptide lack a rigid tertiary structure. In addition, separately or in combination with the above-described tools, a person skilled in the art could also use one of the many available methods for predicting specific antigenic determinants in a polypeptide sequence. See, for example, Hopp, *Pept. Res.* 6:183-90 (1993); Hofmann et al., *Biomed. Biochim. Acta* 46:855-66 (1987); Jameson and Wolf, *Comput. Appl. Biosci.* 4:181-86 (1988); Menendez et al., *Comput. Appl. Biosci.* 6:101-105 (1990); Thornton *et al.*, *EMBO Journal*, 5:409-413, 1986); and Kolaskar *et al., FEBS Lett.* 10:172-4, 1990)). See also Kokolus et al., U. S. Patent No. 5,807,978.

Applicants disagree with the assertion by the Examiner that the present application provides no more than a "mere idea or function" of the polypeptide species within the genus of polypeptides and that "isolation and characterization at a minimum are required" (*see* the Action, page 5). Adequate written description of claims related to a genus of polypeptides does not require that the specific amino acid sequence of each protein itself must be provided. Such a description is not required under 35 U.S.C. § 112, first paragraph, because written description requires neither examples nor an actual reduction to practice. *See Falko-Gunter Falkner v. Inglis,* 448 F.3d 1357, 1366 (Fed. Cir. 2006) ("A claim will not be invalidated on section 112 grounds simply because the embodiments of the specification do not contain examples covering the full scope of the claim language.") ("An actual reduction to practice is not required for written description."). Moreover, in contrast to the present claims, the claims at issue in *The Regents of the University of California v. Eli Lilly and Company* (119 F.3d 1559 (Fed. Cir. 1997)), to which the Action refers, did not recite *any* amino acid or nucleic acid sequence, structure, or formula. The Federal Circuit Court of Appeals, confirming that in *Eli*

Lilly, the term, "human insulin cDNA," conveyed no relevant structural or physical characteristics, further stated that, "[i]t is not correct, however, that all functional descriptions of genetic material fail to meet the written description requirement" (*see Enzo Biochem* at 964; *see also Amgen Inc. v. Hoechst Marion Roussel, Inc.,* 314 F.3d 1313, 1332 (Fed. Cir. 2003)).

Applicants have provided much more than a functional description. As discussed herein, Applicants have described the recited structural features of the polypeptides according to common terminology used in the art (*i.e.,* at least 90% or 95% identity to the full-length amino acid sequence of SEQ ID NO:2), and of chimeric polypeptides comprising antigenic fragments and have correlated those structural features with the recited functional characteristics (*i.e.,* capability to generate antibodies having binding specificity for a polypeptide consisting of the amino acid sequence set forth in SEQ ID NO: 2, and to induce an immune response to *S. pyogenes*). Thus, in view of the state of the art, given the present description and the high skill level, a person skilled in the art could envision and readily predict that many species would be operable other than those disclosed.

Even when a disclosure names a single species, claims to a genus can be supported if the disclosure conveys to a person skilled in the arts the characteristics common to all species (s*ee In re Curtis*, 354 F.3d 1347, 1355 (Fed. Cir. 2004)). An instance in which a disclosure of a single species may not be sufficient under the written description requirement is when the evidence indicates that a person skilled in the art could not predict the operability of ***any*** *species other than the one disclosed. See id.* at 1358. Under this predictability standard, the court in *In re Curtis* rejected appellant's genus claims, declaring that the claims were unsupported by the disclosure of a single species. However, and contrary to the assertion by the Examiner (see Action, page 5, first paragraph), the description relied upon in *In re Curtis* is distinguishable from the present application, in that the description in the Curtis application recited only the common functional properties of the claimed genus and did not provide any structural description of the genus. *See id.* at 1355.

As stated by the court in *In re Angstadt*, the basic policy of the Patent Act is to encourage disclosure (*see In re Angstadt*, 537 F.2d 498, 502-03 (CCPA 1976) ("To require disclosures in patent applications to transcend the levels of knowledge of those skilled in the art would stifle the disclosure of inventions in fields man understands imperfectly.")). The *Angstadt*

court further states that "[d]epriving inventors of claims which adequately protect them and limiting them to claims *which practically invite appropriation of the invention* while avoiding infringement inevitably has the effect of suppressing disclosure." *Id.* at 504 (emphasis added). In the present application, Applicants have sufficiently described the claimed subject matter and described how a person skilled in the art can make and use the claimed compositions comprising polypeptides and chimeric polypeptides as immunogens and vaccines. Given the skill level of a person skilled in the art, the state of the art, and the present disclosure, if the claimed subject matter is limited to compositions comprising a polypeptide with an amino acid sequence of only a single, disclosed sequence, a person skilled in the art can, readily and with trivial effort, *appropriate* compositions that are outside the scope of the claim by using routine, commonly practiced techniques. Such limited scope is not commensurate with Applicants' contribution to the medical art, describing an immunogen that may be useful for treating and preventing *S. pyogenes* infections, and which contribution *does not necessarily rely* on additional common structural features within the polypeptide immunogen.

The specification describes the claimed chimeric polypeptides and compositions comprising polypeptides as recited with sufficient, relevant, identifying characteristics to convey to a person skilled in the art that Applicants possessed the claimed embodiments at the time the application was filed. Applicants therefore submit that the instant claims satisfy the written description requirement under 35 U.S.C. § 112, first paragraph, and respectfully request withdrawal of this rejection.

REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH (ENABLEMENT)

The Examiner rejected claims 21, 23, 24, 36-38, 40, and 42-43 under 35 U.S.C. § 112, first paragraph, asserting that the present claims are not enabled by the teachings in the specification. The Examiner states that the specification is enabling for claims related to a composition and kit comprising a polypeptide that comprises SEQ ID NO:2; however, the Examiner asserts that the specification does not enable compositions comprising polypeptides having 90% or 95% amino acid sequence identity to SEQ ID NO:2. The Examiner also asserts that the specification lacks enabling disclosure for a chimeric polypeptide that comprises an antigenic fragment consisting of 15 consecutive amino acids of SEQ ID NO:2.

Applicants respectfully traverse this rejection and submit that, contrary to the Examiner's assertions, in view of the guidance and direction provided in the specification, the advanced state of the art, and the high level of skill of a person practicing the art, the specification enables a person skilled in the art to make and use the claimed compositions and kits comprising the polypeptides and chimeric polypeptides, as recited, readily and without undue experimentation. (*See In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988)). As noted above with respect to written description, the claimed chimeric polypeptides comprise one, or two or more antigenic polypeptide fragments of a polypeptide consisting of the amino acid sequence set forth in SEQ ID NO:2, wherein the antigenic polypeptide fragments each comprise at least 15 contiguous amino acids of SEQ ID NO:2. As recited in the present claims, an antigenic polypeptide fragment is capable of eliciting an antibody that specifically binds to the polypeptide consisting of SEQ ID NO:2 and is capable of inducing an immune response against *S. pyogenes*. In another embodiment, the present claims relate to a pharmaceutical composition comprising an isolated polypeptide that consists of an amino acid sequence at least 90% identical to the full-length amino acid sequence set forth as SEQ ID NO:2, wherein the isolated polypeptide elicits an antibody that specifically binds to a polypeptide consisting of SEQ ID NO:2 and induces an immune response against *S. pyogenes*.

Also as discussed in detail above in the introductory Remarks (*see* pages 9-11), Applicants disagree with statement in the Action (second full paragraph at page 7), which states that recitation "of the phrase 'an amino acid sequence' reads upon fragments of SEQ ID NO:2, since 15 amino acids from SEQ ID NO:2 is merely one interpretation of 'an amino acid sequence of SEQ ID NO:2.'" Briefly, when claims refer to a polypeptide comprising "*an amino acid sequence* at least 90% identical to the amino acid sequence set forth as SEQ ID NO:2," for example, the polypeptide that comprises *an amino acid sequence at least 90% identical to SEQ ID NO:2* can be no less than 160 amino acids (*i.e.,* 90% of 178 amino acids). To interpret the claim to include smaller polypeptide fragments essentially requires inserting a new phrase as shown in italics: "a polypeptide that comprises an amino acid sequence *of an amino acid sequence* that is at least 90% identical to the amino acid sequence of SEQ ID NO:2." This reading of the claim is contrary to how a person skilled in the art reads the claims and contrary to how the PTO has interpreted such claim language, and is thus improper (see *In re Cortright*, at

1358, *supra*). The following remarks that pertain to these claims and claims dependent thereon are based on the proper reading of the claims.

Given the guidance provided in the specification (including working examples) and the state of the art, the specification teaches a person skilled in the art how to make and use the presently claimed subject matter using nothing more than routine experimentation. For example, the specification teaches an exemplary, detailed polynucleotide sequence and the deduced amino acid sequence of the SHB-GAS-102 polypeptide (*see, e.g.,* SEQ ID NO:1 and SEQ ID NO:2, respectively). Contrary to the Examiner's assertion, the quantity of experimentation required to practice the claimed subject matter is not undue. Although, the claimed genus contains numerous species, the specification as filed provides sufficient guidance with respect to which members of the genus are likely to exhibit both the structural and functional features recited in the claims. The specification describes PCR primers, PCR working conditions, and expression vectors that may be used in isolating and cloning the polypeptide of SEQ ID NO:2, or additional species within the genus of SHB-GAS-102 polypeptides (*see, e.g.,* 48, line 19 through page 54, line 4 (Example 1)). The specification further provides detailed guidance for expressing and purifying the claimed polypeptides (*see, e.g.,* page 59, line 30 through page 61, line 3 (Example 6)).

In addition, a person skilled in the art can, routinely and without undue experimentation, determine whether species within the SHB-GAS-102 polypeptide genus or chimeric polypeptide genus, as recited in the present claims, exhibit the capability to induce an immune response to *S. pyogenes*, and the capability to generate an antibody that specifically binds to a protein consisting of the amino acid sequence of SEQ ID NO:2. As discussed herein, polypeptides can tolerate many substitutions, deletions, and/or insertions, and methods for making and/or identifying variants and for determining their functional activity can be routinely practiced by a person skilled in the art (provided, as is the case here, that an application describes the functional activity and methods for determining the activity). Such experimentation may be accomplished by using immunoassays, screening methods, and animal models described in the application and routinely practiced in the art (*see, e.g.,* page 19, lines 1-11; page 44, lines 24-29; see methods described at page 52, line 26 through page 53, line 24 (Example 1); page 61, line 29

through page 64 (Example 8)). See *In re Wands,* 858 F.2d 731 (Fed. Cir. 1988) ("Enablement is not precluded by the necessity of some experimentation such as routine screening.").

Persons skilled in the immunology art readily appreciate that an advantage of using a polypeptide as an immunogen, when the polypeptide immunogen induces a polyclonal immune response, is that most mutations introduced into the polypeptide when expressed by an infectious disease organism will not destroy all the immunoepitopes that are recognized by antibodies induced by the immunogen. Lipman et al. teach that "because [polyclonal antibodies] are heterogeneous and recognize a host of antigenic epitopes, the effect of change on a single or small number of epitopes is less likely to be significant" (Lipman et al., *ILAR Journal*, 46: 258-268, 261, Col. 1 (2005) (enclosed herewith for the Examiner's convenience)). Indeed, these properties associated with a polyclonal response to an antigen motivate persons skilled in the immunology art to develop vaccines for effectively immunizing individuals against various communicable pathogens.

The Examiner's basis for rejecting the claims for lack of enablement appears to rely, in part, on the possibility that a single amino acid substitution in a SHB-GAS-102 polypeptide might abrogate binding of a specific antibody to that polypeptide. The Examiner extrapolates from examples in the art, which discuss that a single amino acid substitution in a particular protein altered the protein's function, and asserts that making compositions comprising the polypeptides and chimeric polypeptides, as recited, is highly unpredictable (see Action page 8).

Applicants respectfully disagree that Kokolus (U.S. Patent No. 5,807,978) supports the Examiner's assertion that the presently chimeric polypeptides comprising one, or two or more, antigenic fragments of the SHB-GAS-102 polypeptide are not enabled by the specification. Kokolus states that a body of literature suggests that "randomly selected oligopeptides" may rarely elicit high titered antisera (see column 4, lines 8-12). However, a person skilled in the art need not prepare randomly selected oligopeptides from the SHB-GAS-102 sequence (*i.e.,* SEQ ID NO:2), given the knowledge in the art with respect to methods for identifying antigenic regions of a polypeptide. Moreover, Kokolus (issued September 15, 1998) contributed to the state of the art at the time the present application was filed by describing a method that may be routinely performed for identifying immunogenic epitopes on the basis of

the amino acid sequence of a polypeptide. Thus, Kokolus and publications and software programs referred to below describe methods for identifying antigenic epitopes, which may in turn be useful for making, readily and without undue experimentation, SHB-GAS-102 polypeptide fragments that comprise at least one antigenic epitope. Accordingly, the methods and techniques, which are described in the application and/or available and well known to those skilled in the art, may be used to make and practice the claimed subject matter. *See, e.g., Johns Hopkins Univ. v. Cellpro, Inc.*, 152 F.3d 1342, 1360 (Fed. Cir. 1998) ("test [for undue experimentation] is not merely quantitative … if it is merely routine").

Regarding the predictability in the art, Applicants submit that a person skilled in the art recognizes that identifying polypeptides, fragments and variants thereof, that retain their functional characteristics is more predictable than identifying polypeptide species that lose one or more functional characteristics. Even assuming, *arguendo*, that a single conservative point mutation in or near an epitope may abolish binding to an antibody, as asserted by the Examiner (citing Lederman et al., *Mol. Immunol.* 28:1171-81 (1991) and Li et al., *Proc. Natl. Acad. Sci.* 77:3211-14 (1980)), Applicants kindly submit that these studies fail to fairly reflect the "predictability" associated with identifying functional polypeptide variants. To this end, Applicants note that in publishing such studies, few authors report the great number of variants that retain their functional abilities because this data is typically of little interest; compared with identifying variants that have lost function. In practicing the presently claimed embodiments, however, of greater import to a person skilled in the art is the "predictability" of the process of identifying polypeptide variants that retain their recited functional characteristics, information that is not reflected in the studies cited by the Examiner.

A more illustrative example of the "predictability" of identifying functional polypeptide variants may be found in Wan et al. (*Mol. Endocrinol.* 17:2240-50 (2003), submitted herewith) (Wan), which details the process of screening for variants that both retain and lose their function. In particular, Wan prepared a library of 5200 polypeptide variants and detected only 128 (approximately 2.5%) that were *negative* for binding to the relevant monoclonal antibody. Thus, Wan empirically showed that polypeptides can tolerate a great deal of variation, and that making a polypeptide that has lost its described function (in this example, binding to a monoclonal antibody) is far less predictable than identifying polypeptide variants

that *retain* their described function. By quantifying the number of polypeptide variants that retain or lose the ability to bind a specific antibody, Wan reasonably reflects the predictability of the art with regard to the expectation that highly similar polypeptide variants (*i.e.,* 90% or 95% identity to a reference polypeptide) would retain the immunogenic features of that reference polypeptide. In view of this evidence, and given that the polypeptide of SEQ ID NO:2 is capable of eliciting an immune response against *S. pyogenes*, a person skilled in the art would reasonably predict that variants of SEQ ID NO:2 would similarly elicit such an immune response. Thus, according to the teachings in the specification and the knowledge in the art, a person having skill in the art readily appreciates that a polypeptide differing from SEQ ID NO:2 by no more than 5% or 10%, either due to spontaneous mutations occurring in a natural environment or recombinantly introduced mutations, will likely retain the claimed functionality.

In addition, the claimed compositions comprising the polypeptides and chimeric polypeptides are capable of inducing a polyclonal response. Lipman et al. also illustrate the expectations of a person skilled in the art with regard to the predictability of identifying polypeptide variants that retain their recited function, especially in view of the understanding the most antigens elicit a polyclonal response. For example, Lipman *et al.* teach that "because [polyclonal antibodies] are heterogeneous and recognize a host of antigenic epitopes, the effect of change on a single or small number of epitopes is less likely to be significant." Lipman et al., *ILAR Journal*, 46: 258-268, 261, Col. 1 (2005) (enclosed herewith) (emphasis added). Accordingly, the likelihood of producing a functional variant is increased when a polyclonal antibody response is induced.

In addition, if a person skilled in the art so desired to introduce mutations into a SHB-GAS-102 polypeptide, computational methods well known in the art for predicting epitope location can be combined with the teachings in the present application, and the likelihood of producing a polypeptide having the claimed functionality is great. Immunogenic epitopes contained within the SHB-GAS-102 polypeptides can be identified using nothing more than the primary amino acid sequence of those polypeptides. As evidence of the knowledge in the art in this regard, software tools to identify immunogenic epitopes contained within a primary amino acid sequence were well-known in the art long before the filing date of the instant application. For instance, given the exemplary amino acid sequence of SEQ ID NO:2, a person skilled in the

art could use software tools such as PSORT (released in 1991) and Spscan (Wisconsin Sequence Analysis Package, Genetics Computer Group) to predict transmembrane segments and membrane topology of bacterial outer membrane polypeptides. These tools are helpful because a person skilled in the vaccine art understands that immunodominant regions of an antigen are located at exposed areas on the exterior face of the antigen, particularly where loops of polypeptide lack a rigid tertiary structure.

In addition, separately or in combination with the above-described tools, a person skilled in the art could also use one of the many available methods for predicting specific antigenic determinants in a polypeptide sequence. See, for example, Hopp, *Pept. Res.* 6:183-90 (1993); Hofmann et al., *Biomed. Biochim. Acta* 46:855-66 (1987); Jameson and Wolf, *Comput. Appl. Biosci.* 4:181-86 (1988); Menendez et al., *Comput. Appl. Biosci.* 6:101-105 (1990); Thornton *et al.*, *EMBO Journal*, 5:409-413, 1986), Kolaskar *et al., FEBS Lett.* 10:172-4, 1990)). Therefore, the understanding in the art illustrates that a person skilled in the art could use the primary amino acid sequences of SEQ ID NO:2 to identify with reasonable accuracy and predictability, amino acid sequences that comprises immunogenic epitopes.

Applicants need not exemplify every species within a genus, and a person skilled in the art need not make every species to practice the claimed embodiments. As previously made of record, the law is well settled that to satisfy the enablement requirement, an Applicant need not test every embodiment of an invention encompassed by a claim and need not describe a large number of examples, particularly when (as here) the level of skill in the art is high and the teachings of the specification are ample. *See In re Strahilevitz*, 212 U.S.P.Q. 561, 563 (C.C.P.A. 1982) (finding that although the invention encompassed a large variety of compounds, a large number of examples would not be required because examples are not required to satisfy section 112, first paragraph). Moreover, even though a large number of polypeptide variants and chimeric polypeptides may be made, Applicants are not required to list all operable embodiments of the invention and to exclude inoperable ones, if any. *See Atlas Powder Co. v. E. I. Dupont de Nemours & Co.,* 750 F.2d 1569, 1576 (Fed. Cir. 1984).

In the present application, Applicants have provided abundant guidance, including working examples, that teach a person skilled in the art how to make and use the claimed polypeptides and to make and use compositions comprising these polypeptides, for example, as

immunogenic compositions and vaccines, readily and without undue experimentation. Given the skill level of a person skilled in the art, the state of the art, and the present disclosure, if the claimed subject matter is limited to only a single, disclosed sequence, a person skilled in the art can, readily and with trivial effort, *appropriate* polypeptides that are outside the scope of the claim by using routine, commonly practiced techniques. Such limited scope is not commensurate with Applicants' contribution to the medical art, describing an immunogen that may be useful for treating and preventing *S. pyogenes* infections, and which contribution *does not necessarily rely* on the identification of the specific immunogenic epitopes within the polypeptide immunogen.

In view of the guidance provided in the specification, the knowledge and predictability in the art, the presence of multiple working examples, the high level of skill in the art, and the scope of the claims, Applicants submit that a person skilled in the art can practice the presently claimed subject matter readily without undue experimentation. Therefore, the instant claims satisfy the enablement requirement under 35 U.S.C. § 112, first paragraph, and Applicants respectfully request withdrawal of this rejection.

REJECTION UNDER 35 U.S.C. § 102

The Examiner rejected claims 21, 23, and 36-42, under 35 U.S.C. § 102(b), asserting that the claimed subject matter is anticipated by Telford et al. (International Patent Application Publication No. WO 2002/34771) (Telford). The Examiner asserts that Telford teaches a composition comprising a polypeptide represented by "SEQ ID NO:6344" and that the polypeptide has an amino acid sequence that is 100% identical to SEQ ID NO:2. The Examiner also asserts that Telford teaches a chimeric polypeptide comprising antigenic fragments of "SEQ ID NO:6344."

Applicants respectfully traverse this rejection and submit that Telford fails to teach or suggest each feature of the present claims related to chimeric polypeptides, to compositions comprising a polypeptide comprising the amino acid sequence set forth as SEQ ID NO:2 and variants thereof, and to kits comprising the polypeptides. As an initial matter, Applicants respectfully point out that the amino acid sequence of SEQ ID NO:6344 described in Telford relates to a group B streptococcus polypeptide (*see* Telford, page 2319-2320). The

polypeptide having an amino acid sequence set forth in SEQ ID NO:6346 describes a group A streptococcus polypeptide (*see* Telford, page 2320). The sequence alignment presented on page 11 of the Action includes the sequence set forth in SEQ ID NO:6346 and not SEQ ID NO:6344.

Telford fails to teach or suggest a chimeric polypeptide that comprises an antigenic fragment or that comprises two or more antigenic fragments wherein each antigenic fragment consists of at least 15 contiguous amino acids of SEQ ID NO:2. Telford further fails to teach or suggest that such an antigenic fragment is capable of eliciting an antibody that induces an immune response against *S. pyogenes* (also referred to as group A streptococcus (see specification at page 33, lines 15-16)). Telford also fails to teach or suggest a composition comprising an isolated polypeptide that consists of an amino acid sequence at least 90% identical to the full-length amino acid sequence set forth as SEQ ID NO:2 or that comprises an amino acid sequence at least 95% identical to SEQ ID NO:2, and further fails to teach or suggest that the isolated polypeptide of the composition induces an immune response against *S. pyogenes*.

Applicants disagree with the assertion by the Examiner that the cited reference teaches chimeric polypeptides and compositions comprising the polypeptides as presently claimed. Claim 18, to which the Examiner refers (Telford, page 3056, lines 13-15) relates to a hybrid protein that comprises, in part, an amino acid sequence defined in claim 1, which as described at page 5 of the cited reference refers to "a protein of the invention" and *not* to an antigenic fragment. Accordingly, Telford, including claim 18, describes a hybrid polypeptide that comprises any one of the hundreds of full-length polypeptides listed in claim 1 (*see* Telford, page 3024 through page 3031, line 3).

Telford also fails to teach or suggest a kit comprising the chimeric polypeptides or SHB-GAS-102 polypeptides as presently claimed. Telford merely suggests that "streptococcus antigens" can be used in immunoassays and included in kits (*see* Telford, page 27) but fails to teach or suggest that a polypeptide or chimeric polypeptide related to SHB-GAS-102 may be useful as a diagnostic and provided in a kit. Applicants also note that in Telford the claims related to kits comprise oligonucleotides (*see* Telford, page 3056, claims 19-21).

Furthermore, Telford fails as an anticipatory reference because the document fails to provide an enabling disclosure. A person skilled in the art could not have obtained the presently claimed chimeric polypeptides and compositions comprising the SHB-GAS-102

polypeptide, or related species, on the basis of the teachings in Telford without undue experimentation (*see Elan Pharmaceuticals v. Mayo Foundation*, 346 F.3d 1051, 1055 (Fed. Cir. 2003) opining that a "disclosure in an assertedly anticipating reference must be adequate to enable possession of the desired subject matter. It is insufficient to name or describe the desired subject matter, if it cannot be produced without undue experimentation.").

Telford provides more than 5,000 open reading frames that putatively encode polypeptides that are expressed by *S. pyogenes* (also referred to as group A streptococcus) or *S. agalactiae* (also referred to as group B streptococcus) and provides no more than a generalized statement with respect to how the various putatively encoded polypeptides disclosed therein may be used. Telford describes that each and every one of the polypeptides disclosed therein may be a useful antigen for a vaccine or a diagnostic. Given that only a few *S. pyogenes* antigens have been investigated as viable vaccine candidates (*see, e.g.,* specification at page 1, line 30 through page 2, line 20), a person skilled in the microbiology and vaccine arts would immediately understand that the statement in Telford provides no guidance with respect to which polypeptides disclosed therein may be capable of inducing an immune response against *S. pyogenes*. Telford provides no working examples or any data that teach that any of the putative *S. pyogenes* polypeptides may be useful as an immunogen for preventing or treating a *S. pyogenes* infection in direct contrast to the teachings of the present application. Accordingly, given the lack of guidance in Telford, undue experimentation would be required to identify which of any of the *S. pyogenes* polypeptides disclosed therein may be useful as a vaccine or diagnostic.

Applicants therefore submit that the present claims meet the requirements for novelty under 35 U.S.C. § 102 and respectfully request that this rejection be withdrawn.

Applicants respectfully submit that all claims in the application are allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

Respectfully submitted,

SEED Intellectual Property Law Group PLLC

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Enclosures: Supplemental Information Disclosure Statement

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